Impact of intense systemic therapy and improved survival on the use of palliative radiotherapy in patients with bone metastases from prostate cancer

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Received February 16, 2016; Accepted June 27, 2016

DOI: 10.3892/ol.2016.5003

Abstract. More effective drugs may reduce the requirement for palliative external beam radiotherapy for bony target volumes; however, living with metastases for prolonged periods of time may result in more frequent episodes of bone pain or serious skeletal-related events. The purpose of the present study was to evaluate how recent advances in systemic therapy impact radiotherapy utilization. A retrospective analysis of a comprehensive regional database was performed. All oncology care in this region was provided by only one center, assuring complete data. Patients that had succumbed between June 1, 2004 and June 1, 2015 were included. For all 236 patients, the median age at diagnosis of bone metastases was 75 years and median overall survival was 20 months. More intense systemic therapy was associated with a significantly longer survival time. Only 69 patients (29%) did not receive palliative radiotherapy for bony target volumes, whilst 1 course was given to 101 patients (43%), 2 courses to 34 patients (14%) and >2 courses to 32 patients (14%). Radiotherapy was used more frequently in younger patients, those with spinal cord compressions or pathological fractures, and those treated with intense and long-standing systemic therapy. Radiotherapy utilization increased with survival time. For 100 poor-prognosis patients that succumbed within 12 months, 57 courses of palliative radiotherapy were administered, whilst 100 patients that survived for 12-24 months were administered 114 courses (24-36 months, 148 courses). In conclusion, the use of palliative radiotherapy did not decrease when more effective systemic therapy was administered. However, provided that only 5% of patients received radionuclide treatment, additional studies in other populations are required.

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Key words: prostate cancer, bone metastases, chemotherapy, radiotherapy, systemic treatment

Introduction

Metastatic prostate cancer commonly involves the skeleton, resulting in skeletal-related events (SRE), including pathological fractures and metastatic spinal cord compression (MSCC) (1). In addition to systemic treatment, a number of patients also require orthopedic surgery and, in particular, palliative radiotherapy. Systemic treatment options have expanded during the last decade, resulting in improved overall survival rates (2), but it is not entirely clear how these advances impact radiotherapy utilization. More effective drugs may reduce the requirement for radiotherapy; however, living with metastases for prolonged periods of time may result in more frequent episodes of bone pain or other more serious SREs. In a recent meta-analysis, the median survival time of patients with castration-resistant prostate cancer and bone metastases was 21.3 months (3). In a 15-year study from the USA, more than half of patients with bone metastases from prostate cancer had evidence of SREs, either at diagnosis of bone metastases or subsequently (4).

Generally, large databases or cancer registries contain useful data regarding radiotherapy utilization rates. However, there is often a lack of detailed information on systemic therapy and patient-associated baseline data, including comorbidity, blood tests or extent of metastatic disease. Consequently, the comprehensive present study was performed in a patient population treated in a well-defined geographical region with a publicly-funded healthcare system, which provides equal access to treatment, irrespective of income, place of living and other potential socioeconomic barriers. Current radiotherapy utilization rates are important for healthcare authorities and various stakeholders participating in the development of future healthcare services (5,6). An equitable access to specialized healthcare services based on requirements and not on each individual's economy has been a cornerstone in the Norwegian healthcare system. In the present study, the aim of which was to evaluate how recent advances in systemic therapy impact radiotherapy utilization, this aspect is elucidated from the radiotherapy in metastatic prostate cancer perspective.

Patients and methods

Patients and treatment. The present retrospective study included 236 consecutive male patients with bone metastases from prostate cancer, who received oncology care at the Nordland Hospital (Bodø, Norway), which is an academic teaching hospital. These patients succumbed to prostate cancer between June 1, 2004 and June 1, 2015. They were identified from the electronic patient record systems of the hospital and its radiotherapy unit (DIPS®, DIPS ASA, Bodø, Norway; ARIA®, Varian Medical Systems, Inc., Palo Alto, CA, USA). In order to ensure complete follow-up, patients that were alive on June 1, 2015 were excluded from the study.

The National Healthcare System in Norway is the responsibility of the state through state ownership of four regional health authority trusts. Within these, psychiatric and somatic hospitals are organized as health trusts. One of these is the Nordland Hospital Trust (Bodø, Norway), which provides oncology services to the complete population of the Nordland county, a geographically large, but sparsely populated, area (38,460 km^2; 241,682 inhabitants). Municipalities are responsible for primary healthcare, and there are no private practices providing cancer treatment in the county. There are three centers that have radiation treatment facilities in the northern and central region of Norway (Bodø, Tromsø and Trondheim), one of which is The Nordland Hospital, which are separated by large distances; therefore, dilution effects, where a patient receives radiotherapy at other centre, does not apply in the collection of reliable data if the study population lives within close proximity to one of the centers. One of these centers is The Nordland Hospital, which forms the basis of the present and previous analyses (7).

Since the present study was a retrospective quality of care analysis, no approval from the Regional Committee for Medical and Health Research Ethics was required. Similarly no approval from the Norwegian Social Science Database had to be obtained.

Blood and imaging tests. Serum prostate-specific antigen (PSA), radioisotope bone scan and computed tomography (CT) of the chest, abdomen and pelvis were part of routine blood chemistry and imaging assessment in patients with metastatic prostate cancer, which were performed every three months. To confirm suspicious findings, ultrasound and/or magnetic resonance imaging were performed. Positron emission tomography was not available.

Statistical analysis. All analyses were performed with SPSS version 22 (SPSS IBM, Armonk, NY, USA). Actuarial survival data from imaging diagnosis of bone metastases was calculated using the Kaplan-Meier method, and compared between different groups with the log rank test. The date on which the patients succumbed was recorded. Associations between different variables of interest were assessed using χ^2 or Fisher's exact probability tests (two-tailed). $P \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The median age at diagnosis of bone metastases was 75 years (range, 56-94 years). A total of 81 patients (34%) had bone metastases at the time of diagnosis with prostate cancer. The majority (n=155; 66%) had metachronous metastatic disease following a median of 67 months from initial cancer diagnosis. In total, 49 patients that had metastatic disease were diagnosed with bone metastases prior to the development of castration-resistant prostate cancer (CRPC), and 101 patients already had CRPC (unknown data in the remaining 5 patients). In patients with CRPC, the median time interval between the start of endocrine treatment and diagnosis of bone metastases was 38 months. Only

Table I. Patient characteristics at time of diagnosis with bone metastases (n=236).

Parameter	n (%)
Marital status	
Married/partner	176 (75)
Single	51 (22)
Unknown	9 (4)
Residence	
Bodø[a]	112 (48)
Surrounding communities[b]	124 (53)
Charlson comorbidity index	
0	109 (46)
1	68 (29)
2	31 (13)
>2	15 (6)
Unknown	13 (6)
Gleason score	
≥8	100 (42)
<8	83 (35)
Unknown	53 (23)
NCCN risk category at first cancer diagnosis	
M1	81 (34)
N1	13 (6)
High	97 (41)
Intermediate	24 (10)
Unknown	21 (9)
Initial treatment strategy	
Surgical treatment	14 (6)
Radiotherapy ± endocrine treatment	14 (6)
LHRH agonist	116 (49)
Antiandrogen	23 (10)
Orchiectomy	10 (4)
Watchful waiting	59 (25)
Bone metastases (isotope bone scan)	
1	18 (8)
2-4	52 (22)
5-10	50 (21)
>10 or super scan	99 (42)
Unknown	17 (7)

[a]~50,000 inhabitants; [b]~70,000 inhabitants. NCCN, National Comprehensive Cancer Network; LHRH, luteinizing hormone-releasing hormone.

Table II. Systemic therapy following diagnosis of bone metastases (n=236).

Treatment	n (%)
Chemotherapy type[a]	
None	149 (63)
One line	46 (20)
Two lines	27 (11)
Three lines	14 (6)
Chemotherapy drug[a]	
Taxotere	79 (34)
Mitoxantrone	9 (4)
Cabazitaxel	5 (2)
Abiraterone	28 (12)
Enzalutamide	10 (4)
None	105 (44)
Bisphosphonates/denosumab treatment	
None	111 (47)
Monthly zoledronic acid	98 (42)
Monthly denosumab	23 (10)
Other bisphosphonate	4 (2)
Overall systemic therapy	
None	94 (40)
Bone-targeted	55 (23)
Chemotherapy[a]	17 (7)
Both	70 (30)
Radionuclide therapy	
None	225 (95)
Radium-223	6 (3)
Other	5 (2)

[a]Includes cytotoxic chemotherapy, abiraterone and enzalutamide.

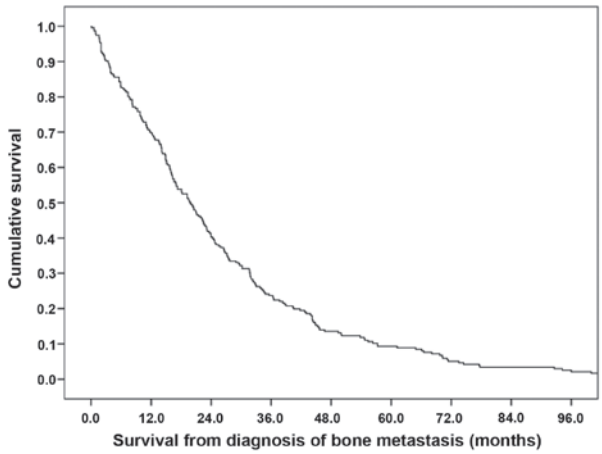

Figure 1. Overall survival time of patients with bone metastasis from prostate cancer (n=236).

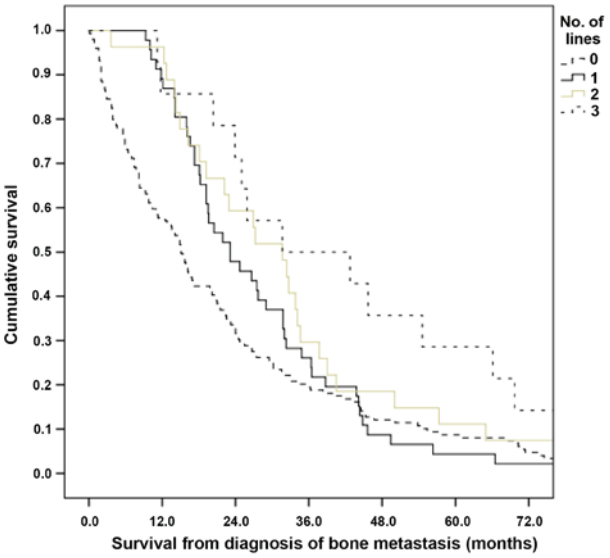

Figure 2. Overall survival time of patients with bone metastasis from prostate cancer stratified by systemic therapy (P=0.01; pooled over all strata). Median values were 15.1, 23.1, 31.7 and 31.7 months for patients not treated and treated with 1, 2 or 3 lines of chemotherapy, respectively.

49 patients (21%) had other distant metastases, including to the liver or non-pelvic lymph nodes, when they were diagnosed with bone metastases. The median PSA level was 78.5 μg/l (range, 0.9-10,302.0 μg/l; normal range, <4 μg/l). Additional information is shown in Table I.

Systemic treatment. The treatment regimes used to treat the present patients with bone metastases evolved in line with the approval of novel drugs in Norway. In general, adherence to national guidelines is extremely high throughout the country (8). The patients did not participate in clinical trials or early access programs. Early during the study period (2004-2011), a typical patient received endocrine therapy, including total androgen blockade, followed by anti-androgen withdrawal. Following the development of CRPC, patients were treated with prednisolone and taxotere, which may have been followed by mitoxantrone. Later in the study period (2012-2015), cabazitaxel, abiraterone and enzalutamide became available. All patients were continued on luteinizing hormone-releasing hormone agonists, unless orchiectomy had been performed. Individualized decisions were made regarding the sequence of treatments. Additional information is shown in Table II.

Survival and other endpoints. Median overall survival was 20 months (Fig. 1). More intense systemic therapy was associated with longer survival time over all strata (Fig. 2; P=0.01). Median values were 15.1, 23.1, 31.7 and 31.7 months for patients not treated and treated with 1, 2 or 3 lines chemotherapy, respectively. In order to reduce selection bias, a landmark analysis was performed, which included only patients alive 3 months following diagnosis of bone metastases. This confirmed the initial results; median survival was 17.0, 23.1, 31.7 and 31.7 months for patients not treated and treated with 1, 2 or 3 lines, respectively.

A total of 12 patients (5%) had pathological fractures or MSCC as the first sign of bone metastases. Overall, 44 patients (19%) developed pathological fractures [MSCC, 35 patients (15%)] during follow-up. In the majority of cases, fractures developed prior to the initiation of bisphosphonates or denosumab treatment (n=28). The median time between diagnosis of bone metastases and treatment with bone-targeting drugs was 6 months. A minority of patients (32%) that succumbed

Table III. Radiotherapy utilization, including external beam and skeletal target (n=236).

	Courses of radiotherapy, n (%)					
Parameter	0	1	3	≥3	P-value	Median target volumes[a]
Age, years						
<75	21 (20)	42 (40)	14 (13)	28 (27)		2.0
≥75	48 (37)	59 (45)	20 (15)	4 (3)	<0.0001	1.0
Initial symptom						
MSCC/PF	0 (0)	5 (42)	3 (25)	4 (33)		2.0
Other	69 (31)	96 (43)	31 (14)	28 (13)	0.0100	1.0
MSCC/PF[b]						
Not present	67 (40)	65 (39)	22 (13)	14 (8)		1.0
Present	2 (3)	36 (53)	12 (18)	18 (26)	<0.0001	2.5
Chemotherapy[c]						
No chemotherapy	57 (38)	64 (43)	22 (15)	6 (4)		1.0
One line only	6 (13)	21 (46)	8 (17)	11 (24)		2.0
Two lines	5 (19)	10 (37)	4 (15)	8 (30)		2.0
Three lines	1 (7)	6 (43)	0 (0)	7 (50)	0.0001	2.5
Overall systemic therapy[d]						
None	51 (54)	34 (36)	10 (11)	0 (0)		0
Bone-targeting	6 (11)	31 (56)	12 (22)	6 (11)		2.0
Chemotherapy	8 (50)	5 (31)	1 (6)	2 (13)		0.5
Both	4 (6)	31 (44)	11 (16)	24 (34)	0.0001	2.0
Survival, months						
<12	30 (42)	32 (45)	8 (11)	1 (1)		1.0
12-24	20 (28)	33 (46)	10 (14)	9 (13)		1.0
24-36	12 (31)	12 (31)	6 (15)	9 (23)		2.0
36-48	4 (17)	10 (42)	4 (17)	6 (25)		2.0
>48	3 (10)	14 (47)	6 (20)	7 (23)	0.0100	2.0

[a]All courses combined. [b]Between diagnosis of bone metastases and death. [c]Includes cytotoxic chemotherapy, abiraterone and enzalutamide. [d]Includes cytotoxic chemotherapy, abiraterone, enzalutamide, bisphosphonates and denosumab. MSCC/PF, metastatic spinal cord compression/pathological fracture.

within 12 months were prescribed bone-targeting drugs. This figure increased to 57% in patients surviving 12-24 months, 69% in patients surviving 24-36 months, and 63% in those surviving >36 months.

Palliative external beam radiotherapy to skeletal target volumes. Three common fractionation regimes were prescribed: 8 Gy single fraction; 5 fractions of 4 Gy; and 10 fractions of 3 Gy. Stereotactic radiotherapy was not available. In total, 69 patients (29%) did not receive radiotherapy. One course of radiotherapy was administered to 101 patients (43%), two courses to 34 patients (14%), three courses to 20 patients (9%), and more than three courses to 12 patients (5%). One target volume was irradiated in 56 patients (24%), two in 50 patients (21%), three in 24 patients (10%), four in 13 patients (6%), and more than four in 24 patients (10%).

Predictors of radiotherapy utilization (Table III). All aforementioned baseline characteristics and systemic therapy regimens were analyzed. No association was identified between radiotherapy utilization and the number of bone metastases at diagnosis of metastatic disease, synchronous vs. metachronous metastases, distance to radiotherapy center and the majority of other parameters. Radiotherapy was utilized more frequently in patients <75 years of age, patients with MSCC or pathological fracture as a first sign of bone metastases, and patients that developed MSCC or pathological fractures during the disease trajectory. Significant associations were also observed with regard to the number of lines of systemic treatment, and whether or not such treatment included various types of drugs. In general, patients with intense and long-standing systemic therapy also required more palliative radiotherapy (Table III).

Radiotherapy utilization increased with increasing patient survival time. Based on the results in Table III, utilization rates were calculated per 100 patients. For 100 poor-prognosis patients, who succumbed within 12 months, 57 appointments (or courses) for a consultation with a radiation oncologist, treatment planning and palliative radiotherapy were required.

For 100 patients surviving 12-24 months, the corresponding figure was 114 appointments (24-36 months, 148 appointments; 36-48 months, 179 appointments; >48 months, 170 appointments).

Discussion

Recently, several novel systemic treatment options for patients with metastatic and/or CRPC have become available, the first being docetaxel (9). A retrospective study of CRPC patients treated with palliative radiotherapy for bony target volumes in BC, Canada, compared patients in the pre-docetaxel era (radiotherapy between 1998 and 2001) to those in the docetaxel era (radiotherapy between 2006 and 2009) (10). In that study, time of the first radiotherapy treatment to bone was used to select patients at a similar point in their disease state (i.e., onset of bone pain). The primary objective was to determine the median survival in the two eras; of the 919 patients in the pre-docetaxel era and the 957 in the docetaxel era, 7 and 37% received docetaxel, respectively, compared with 34% in the present study. The median survival time from the first palliative radiotherapy was 7.5 vs. 10.3 months (P<0.0001). Therefore, that study demonstrated that docetaxel improves survival time at a population level. By contrast, in a randomized trial (9), the effect of docetaxel treatment was moderate. Approximately the same magnitude of improvement in patient survival time was observed with cabazitaxel (11), abiraterone (12,13) and enzalutamide (14,15) treatment, although efficacy varied between post- and pre-chemotherapy settings. More effective drugs may reduce the requirement for palliative radiotherapy; however, living with metastases for prolonged periods of time may result in more frequent episodes of bone pain or other SREs treated with radiotherapy. The impact of altering treatment paradigms on radiotherapy utilization should be monitored regularly in order to adjust the necessary resources.

Radiotherapy utilization was the main endpoint of the present study. The secondary results from the present study were consistent with those of the landmark randomized trials (9,11,12,14); there was a prolongation of survival time with more available lines of therapy. However, it is important to note that the present patients differed from those included in the previous trials, such as differences between disease stage at bone metastases diagnosis. The present study included patients with primary metastatic disease (hormone sensitive) and secondary metastatic disease (prior to or following the development of CRPC), irrespective of performance status and prognosis. The role of performance status was not analyzed, since this variable alters unpredictably during the disease trajectory, such as following successful palliative radiotherapy. In addition, it is important to emphasize the limited sample size and statistical power of the present study. A larger study based on cancer registry data would have been possible. However, such registries collect fewer data concerning baseline characteristics and details of systemic therapy. Therefore, important insights are derived from smaller, but nevertheless population-based, studies.

Using the Surveillance, Epidemiology, and End Results-Medicare linked database, Murphy *et al* (16) analyzed patients with stage IV breast, prostate, lung or colorectal cancer diagnosed between 2000 and 2007, and observed these patients until 2009. A total of 41% of the study population received palliative radiotherapy, including 53% of patients with lung cancer, followed by those with breast (42%), prostate (40%), and colorectal cancers (12%). The present study observed a higher utilization rate of 71%. However, the health care system in the present study is different. The study by Murphy *et al* revealed that older patients and those with higher Charlson comorbidity scores were significantly less likely to receive palliative radiotherapy (16). Regarding age, comparable results were obtained to the present study, but comorbidity was not significant. As one would expect, patients with MSCC and/or pathological fractures were more likely to receive radiotherapy (97 vs. 60%).

The present study identified that patients with intense and long-standing systemic therapy also required more palliative radiotherapy. Radiotherapy utilization increased with increasing survival time. For 100 poor-prognosis patients, who died within 12 months, 57 appointments for consultation with a radiation oncologist, treatment planning and palliative radiotherapy were registered. For 100 patients surviving 12-24 months, the corresponding figure was 114, which is twice as high; however, with a longer survival time, the relative increase diminished (24-36 months, 148; 36-48 months 179; >48 months, 170). A possible explanation is the increasing use of bone-targeting drugs in patients with improved survival. Such drugs were prescribed in 32% of patients that succumbed within 12 months. This figure increased to 57% in patients surviving 12-24 months and 69% in patients surviving 24-36 months. It is well known that bone-targeting drugs significantly reduce the incidence of SREs (17). This effect has also been demonstrated for another novel systemic treatment options, including radionuclide treatment with the α-emitter radium-223 (18-20). In addition, survival improved significantly with radium-223 treatment compared with placebo (18). However, only 5% of the present patients received radionuclides; therefore, it is necessary to perform additional studies in patients treated with radium-223 and to update radiotherapy utilization rates as novel treatment options become available and others alter. For example, taxotere is currently used at diagnosis of metastatic disease rather than following the development of CRPC (21).

In conclusion, the present study demonstrated that the use of palliative radiotherapy did not decrease when more effective systemic therapy was administered. Palliative radiotherapy remains an important part of the multimodal management of patients with skeletal metastases from prostate cancer.

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